REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the following remarks. The Office Action incorrectly states that Claims 1-36 are pending. The Office Action fails to recognize the Preliminary Amendment (copy enclosed) filed concurrently with the patent application. The filing receipt for this application correctly shows 43 claims as pending. The Preliminary Amendment amended Claims 4, 9, 15, 17, 20, 23, 26, 27, and 29-37, cancelled Claim 38 and added new Claims 39-43. Applicant requests that the Preliminary Amendment be considered.

Applicant believe that Claims 1-22, 29-31, 33-37 and 39-43 properly are pending in this application. Applicant is amending herewith Claims 1, 3, 7, 20, 39 and 40; applicant is canceling herewith Claim 2. Following entry of the foregoing amendments, Claims 1, 3-22, 29-31, 33-37 and 39-43 will be pending.

The Office Action:

Claims 9-12, 14-22, 29-31 and 33-36 were objected to as being in improper form because of being improper multiple dependent claims. Claims 16 and 19 were also objected to as not conforming to the Sequence Rules and Regulations. Claims 7 and 8 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-3, 7 and 8 were rejected under 35 U.S.C. § 102(b) as being completely anticipated and unpatentable over the article by Young et al. Claims 1-8 and 13 were rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over the published patent application to Epenetos et al. (WO

94/15644) in view of the article by Schlom, the article by Van Hoff et al. and the article by Verhoyen et al. Applicant respectfully traverses the foregoing rejections.

Priority and Oath/Declaration:

Acknowledgement was made of the claim of priority to GB 0008049.9 filed April 3, 2002. However, the examiner could not locate a copy of the application or a patent issued therefrom. The Office Action further states that the Oath is defective because of the claim of priority to GB 0008049.9. The Office Action states that submission of the priority application could overcome the objection. Applicant is submitting herewith a certified copy of GB 0008049.9 filed April 3, 2002. In view of the foregoing, applicant submits that the Oath is not defective and priority to GB 0008049.9 should be granted.

Claim Objections:

Claims 9-12, 14-22, 29-31 and 33-36 were objected to as being in improper form because of being improper multiple dependent claims. In the Preliminary Amendment, the multiple dependent claims were eliminated. There are no multiple independent claims presently pending. Therefore, this objection is improper and should be withdrawn.

Claims 16 and 19 were also objected to as not conforming to the Sequence Rules and Regulations. The rejection states that Sequence identifiers are required for Claim 16 and the "GSGG" peptide of Claim 19. Applicant is amending herewith Claims 16 and 19 to include the proper Sequence identifiers.

Rejection Under 35 U.S.C. §102:

Claims 1-3, 7 and 8 were rejected under 35 U.S.C. § 102(a) as being completely anticipated and unpatentable over Young, *Proceed Amer Assoc Cancer Res*, March 2000; 41:289 ("Young"). The rejection states that Young discloses an immunotoxin comprising humanized HMFG1 and Dnase I and therefore anticipates claims 1-3, 7 and 8.

35 U.S.C. § 102(a) states: "A person shall be entitled to a patent unless –

(a) the invention was known or used **by others** in this country or patented or described in a printed publication in this or a foreign country before the invention thereof by the applicant for patent" (emphasis added)

The courts have ruled that "one's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar." *In re Facius*, 408 F.2d 1396, 161 USPQ 294, 301 (CCPA 1969).

Similarly, applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). *see* MPEP 2132.01 citing *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

The applicant encloses a Declaration under 37 C.F.R. § 1.132 stating that the reference indicates on its face that it was authored by the inventive entity named in the application under examination. Therefore the article by Young cannot be used to reject the claims under 35 U.S.C. § 102(a).

Rejection Under 35 U.S.C. §103:

Claims 1-8 and 13 were rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over the published patent application to Epenetos et al. (WO 94/15644) in view of *Molecular Foundations of Oncology*, 1991, pp. 95-134 ("Schlom"), *Cancer Res* 1996, 56:5179-5185 ("Van Hof") and WO 92/04390 ("Verhoyen"). The rejection states that it would be obvious to combine the disclosure of Epenetos with Schlom, VanHof and Verhoyen to arrive at the claimed HMGF1-DNAse fusion compound and use in the preparation of a medicament for treatment in a mammal.

The Legal Standard

The Examiner's own Manual of Patent Examining Procedure (MPEP) clearly describes the criteria for establishing a *prima facie* case of obviousness.

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves of in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectations of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." s*ee* MPEP 2143.

The Prior Art

Epenetos

Epenetos discloses immunoconjugate compounds comprising a target cell specific portion and a cytotoxic portion. The disclosure of Epenetos includes the cytotoxic portion being an endonuclease and the target to which the target cell-specific portion binds as HMFG1 (also known as PEM). As the examiner has acknowledged, Epenetos does not disclose the specific combination of **humanized** HMFG1 and an endonuclease.

Schlom

Schlom discloses the humanization of antibodies and describes the pros and cons of internalization of immunoconjugates. Schlom states on page 107 (right column, lines 5-10) that it is necessary for an immunoconjugate to be internalized by the target cell in order

to produce a satisfactory efficacy of the conjugated drug but that the internalization step is a **limitation** to the use of immunoconjugates.

Instead, Schlom proposes that an alternative method to overcome this limitation is for the immunoconjugate to dissociate at the target cell periphery and the cytotoxic agent to then be transported into the cell.

Furthermore, on page 108 (left column) Schlom discusses the results of a number of studies on antibody-drug immunoconjugates. Each of the immunoconjugates discussed related to the use of the cytotoxic agent ricin A.

Schlom fails to indicate any cytotoxic agent, other than ricin A, as being suitable for conjugation. As such, the skilled person would not consider it obvious to replace an effective cytotoxic agent with an agent (such as an endonuclease) that is neither discussed nor hinted at being cytotoxic by Schlom.

Hence, Schlom teaches away from the use of internalizing immunoconjugates possessing an endonucleolytic portion and a skilled person would not seek to apply the disclosure of Schlom to the teaching of Epenetos because the two teaching s are incompatible with each other.

Van Hof

Van Hof describes a study of the anti-PEM antibody humanized CTMO1 (hCTMO1) in ovarian cancer. Van Hof discloses that PEM is continually internalized and recycled. However, Van Hof also states in the same sentence that PEM is "shed into the

circulation, where it can be measured using one of the double-determinant commercially available CA15-3 assays."

A skilled person would understand from the statement that only a proportion of PEM is internalized into the cell (irrespective of the efficiency of localization to tumor sites) and as such is not an appropriate target for an immunoconjugate requiring internalization.

Furthermore, claim 1 has been amended to define the target cell-specific portion is humanized HMFG1 antibody or an antigen-binding fragment thereof. Van Hof discusses the superior results (see abstract) that the anti-PEM antibody hCTMO1 exhibits over other anti-PEM antibodies in localizing cytotoxic compounds to tumor sites (which is different from cell internalization). From the teaching of Van Hof, if a skilled person overcame their hesitation to use PEM as a target then they would be directed towards the use of the "superior" hCTMO1 antibody instead of the claimed HMFG1 antibody.

Therefore, van Hof teaches away from the use of any anti-PEM antibody other than and as such, a skilled person would not seek to combine the teaching of van Hof with the teaching of Epenetos.

Verhoyen

Verhoyen discloses methods of humanization of HMFG1 antibodies. However, Verhoyen neither discloses nor indicates the possibility of conjugating HMFG1 to a compound possessing endonucleolytic activity. On page 9 (practical applications of the invention), it is indicated that the humanized HMFG1 can be linked to another agent.

However, on page 10, lines 1-6, these other agents are qualified as the established anti-cancer agents: radioisotopes, chemotherapy drugs such as methotrexate, ricin toxin and enzymes that activate other drugs. As such there is no indication that an endonuclease is desirable to use in combination with HMFG1.

The discussion in Verhoyen of ricin A as a compound for use in an immunoconjugate supports (and is supported by) the disclosure of Schlom (p. 108) which discloses the use of ricin in its discussion of experimental studies of ricin. As such a skilled person would seek to explore possible improvements to ricin immunoconjugates and not the use of endonucleases.

The cited art is deficient in providing the motivation to combine the cited references and in fact teaches away from combination to arrive at the claimed compound and method of use. Absent the teachings of the present specification, one of skill in the art would not be motivated to combine the cited references to arrive at the claimed compound and method of use without undue experimentation.

Claims 1-7 and 13 were rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over Epenetos et al. (WO 94/15644) in view of Pietersz.

The Prior Art

Epenetos

Epenetos has been described previously.

Pietersz

Pietersz describes a study of the biological characteristics of the anti-PEM antibody hCTMO1. In particular Pietersz studied the amounts of internalization and tumor localization of hCTMO1 in comparison to the murine anti-PEM antibody BC-2.

The experimental results produced by Pietersz show hCTMO1 to be significantly more effective than BC-2 at both internalization (70% compared to 60%) and localization (68% compared to 28%).

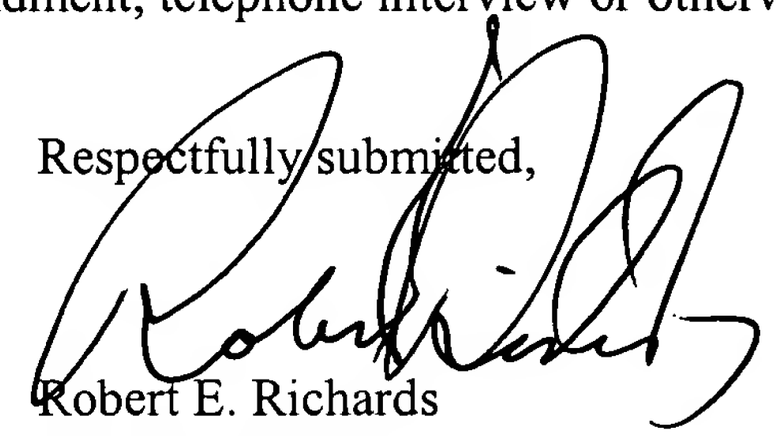
As such, Pietersz discloses that the hTCMO1 antibody is highly desirable for use in localization to and internalization by tumor cells and as such hCTMO1 is the direction in which further work anti-PEM antibody work should be taken. There is no suggestion nor indication that humanized anti-PEM antibodies in general, let alone the HMFG-1 antibody, exhibit improved internalization.

Furthermore, the only indication of use of hCTMO1 as an immunoconjugate is with the drug Idarubicin. As such, Pietersz does not disclose the benefits of using any anti-PEM antibody other than hCTMO1 nor the use of an endonuclease, i.e. the teaching of Pietersz is two steps removed from the present invention. Therefore, a skilled person would not consider combining the teaching of Epenetos with the unrelated teaching of Pietersz in order to arrive at the present invention.

Conclusion

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and remarks. Such action is courteously solicited. Applicant further requests that the Examiner call the undersigned counsel if allowance of the claims can be facilitated by examiner's amendment, telephone interview or otherwise.

Respectfully submitted,



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